SIALIC ACID TRANSPORTER PROTEINS AS BIOMARKERS AND DRUG TARGETS

[0001] The present invention relates to a biomarker and/or drug target for mucosal diseases.

[0002] Although the following description refers exclusively to biomarker/drug target for inflammatory bowel disease (IBD), the person skilled in the art will appreciate that the invention can be used as a biomarker and/or drug target for a number of mucosal diseases and is not limited to a faecal biomarker or drug target for inflammatory bowel diseases.

[0003] IBD which includes Crohn's disease (CD) and ulcerative colitis (UC) is characterised by chronic inflammation of the gastrointestinal (GI) tract which is associated with changes in the gut microbiome. Characteristics of faecal microbiota are attractive biomarkers in IBD because they provide a non-invasive way to monitor changes in the intestinal environment associated with mucosal inflammation. Microbial biomarkers do not necessarily play a causative role in disease. The appearance or disappearance of a microbial group may rather be related to how well the organism can compete in the altered intestinal environment in disease.

[0004] IBD is characterised by changes in mucin glycosylation (i.e. decrease in complex mucin glycan, increased sialylation) and dysbiosis (changes in microbiota composition). Several metagenomics studies have shown a disproportionate increase in certain mucosa-associated bacteria such as *Ruminococcus gnavus* in IBD. As stated above faecal microbiota are attractive biomarkers because they provide a non-invasive way to monitor changes occurring at the mucosal interface.

[0005] The use of microbe signatures as biomarkers is currently hampered by the phylogenetic resolution achievable by 16S rRNA which does not allow distinguishing between strains and origin (luminal vs mucosal compartment). As such, there are currently a number of biomarkers in clinical use but no single one can reliably diagnose IBD or sub-classify cases of IBD into UC or CD. The significance of leaving patients without a clear diagnosis is the potential adverse impact on future management. Endoscopy evaluation is currently viewed as the nearest to a 'gold standard' tool, however it is often unattractive to patients in terms of comfort and convenience. In addition, colonoscopy may present some significant risk such as perforation. It is estimated that up to 50% of patients with gastrointestinal symptoms are referred for unnecessary endoscopic investigation.

[0006] Faecal biomarkers represent an attractive non-invasive alternative indicator of IBD since they are more acceptable to patients and easier to perform in everyday clinical practice. To date, faecal markers include a biologically heterogeneous group of substances that either leak from or are actively released by the inflamed mucosa (such as calprotectin or lactoferrin) but these biomarkers are not specific for IBD or cannot distinguish between UC and CD.

[0007] It is therefore an aim of the present invention to identify a microbial gene the presence of which can be utilised to address the abovementioned problems.

[0008] It is a further aim of the present invention to provide a method of identifying and/or inhibiting a transporter protein to address the abovementioned problems.

[0009] It is a yet further aim of the present invention to provide a microbial-derived faecal biomarker which addresses the abovementioned problems.

[0010] In a first aspect of the invention there is provided a method of identifying, monitoring and/or diagnosing mucosal bacterial presence or infection, said method including the step of detecting at least part of a sialic acid transporter protein encoded by *Ruminococcus gnavus* (*R. gnavus*) ATCC 29149 Nan cluster.

[0011] Typically the transporter protein is specific to 2,7-anhydro-Neu5Ac.

[0012] In one embodiment the substrate or solute binding protein of the ATCC 29149 Nan cluster is encoded by RUMGNA_02698.

[0013] Typically the transporter protein is used as an indicator or biomarker for inflammatory bowel disease. Further typically the transporter protein is used as a faecal biomarker.

[0014] In one embodiment the presence of the transporter protein is used as an indicator of likelihood of success of microbiome-targeted therapies such as faecal microbiota transplantation.

[0015] In one embodiment polymerase chain reaction (PCR) is used to amplify the protein and/or identify the presence of the transporter protein. Typically quantitative polymerase chain reaction (qPCR) is used to identify the presence of the protein.

[0016] In one embodiment the presence or absence of the transporter protein is used to distinguish or diagnose UC or CD.

[0017] In a second aspect of the invention there is a method of inhibition of the growth of bacterium, said method including the step of inhibition of a sialic acid transporter protein.

[0018] Typically the bacterium is *Ruminococcus gnavus, Blautia obeum* or *Streptococcus pneumoniae.*

[0019] Preferably the bacterium is *R. gnavus.*

[0020] Typically the transporter protein is encoded by ATCC 29149 Nan cluster.

[0021] Typically the transporter protein is specific to 2,7-anhydro-Neu5Ac.

[0022] In one embodiment the substrate or solute binding protein of the ATCC 29149 Nan cluster is encoded by RUMGNA_02698.

[0023] In one embodiment the transporter (SBP) is not the only gene-specific to *R. gnavus* Nan cluster, typically the RgOx is also specific to the peculiar cluster as needed to convert 2,7-anhydro-Neu5Ac to Neu5Ac once inside the cell.

[0024] Further typically, a biomarker could be either RgSBP or RgOx, or the whole cluster of genes.

[0025] In a third aspect of the invention there is provided a method of treatment of a mucosal disease in a subject comprising administering a therapeutically effective amount of a transport protein inhibitor.

[0026] In a further aspect of the invention there is provided a pharmaceutical composition including a transport protein inhibitor.

[0027] Typically the transporter protein is specific to 2,7-anhydro-Neu5Ac.

[0028] Further typically the inhibition is by direct or indirect inhibition.

[0029] The skilled person will appreciate the advantages over current methods is that, without being invasive, the